IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Nobuyuki TAKAKURA et al.

Application No.: 10/584,028 Confirmation No.: 4443

Filed: June 22, 2006 Art Unit: 1651

For: INDUCTION OF MYOCARDIAL CELL FROM MAMMALIAN BONE-MARROW CELL OR CORD BLOOD-DERIVED CELL AND FAT TISSUE Examiner: T. Kim

DECLARATION UNDER 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

1. I, Nobuyuki Takakura, am a co-inventor of the present application.

2. I understand that it is the Examiner's position that U.S. 2002/0142457 to Umezawa *et al.* ("Umezawa") in view of Rangappa *et al.*, *Ann. Thorac. Surg.*, 2003, 75:775-779 ("Rangappa"), Egger *et al.*, *Nature*, 2004, Bonnet *et al. Clin. Exp. Med.*, Gilmore *et al. Exp. Hematol.*, 2000, and Lee *et al.*, *Blood*, 2004, render the instant claims obvious.

3. The Examiner believes that an ordinary artisan would have been motivated to combine the bone marrow or cord blood derived multipotential stem cells described in Umezawa with the fat-derived stem cells of Rangappa to induce myocardial differentiation and achieve the claimed method. The Examiner makes this assertion because he believes that the method of

differentiating bone-marrow or cord blood-derived stem cells into cardiomyocytes, as described in Umezawa, is identical to the method of differentiating the fat-derived stem cells, as described in Rangappa. According to the Examiner, since both bone marrow stem cells and fat-tissue derived stem cells can be differentiated into cardiomyocytes upon treatment with 5-azacytidine, an ordinary artisan would have been motivated to combine the two stem cell populations. Although the Examiner's reasoning for combining the two cell populations is different from those of the inventors, the same result would allegedly be achieved, *i.e.*, bone marrow stem cells would predictably differentiate into cardiomyocytes, *see* Office Action of June 30, 2009.

4. Umezawa teaches that cardiomyocytes may be used for heart regeneration or to treat heart disease, *see* paragraph [0151] to [0153] of Umezawa. For example, Umezawa indicate that bone marrow stem cells, which differentiate into sinus node cells, may be useful for therapeutic purposes, *see* paragraph [0153]. Rangappa indicate that differentiated cardiomyoctyes may be used for transplantation into the heart, *see* page 779 of Rangappa, left column. Both Umezawa and Rangappa warn that different results can be obtained if the cells are not used after a certain point in differentiation. For example, if sinus node cells are desired, further differentiation should not be allowed to occur because the cells can subsequently differentiate into ventricular cardiomyocytes, *see* paragraph [0134] of Umezawa. Rangappa warns that if the cells are to be transplanted, transformation should occur within one week after differentiation to avoid dedifferentiation in the culture, *see* page 779 of Rangappa, left column.

5. However, the fat-derived stem cells described in Rangappa appear to differentiate into cardiomyocytes at a different rate than the bone marrow stem cells derived in Umezawa. Umezawa describe that under optimal conditions, *i.e.*, 3 μmol/l of 5-azacytidine, cells derived from bone marrow spontaneously beat two weeks after induction, *see* Example 1 of Umezawa.

6. In contrast, fat-derived stem cells under optimal conditions, *i.e.* at 9 μmol/L of 5-azacytidine, spontaneously beat three weeks after induction, *see* pages 777-778, bridging paragraph. Accordingly, there would not be any motivation for an ordinary artisan to combine

the stem cell populations into a single culture because the bone marrow stem cells could dedifferentiate or differentiate into another cell type by the time the fat-derived stem cells were at a stage useful for transplantation, rendering the bone marrow differentiated cells unsuitable for their intended purpose.

7. Further, it does not appear from the cited references that an ordinary artisan could have reasonably predicted that combining bone marrow stem cells and fat-derived stem cells, using known methods, *i.e.*, 5-azacytidine treatment, would have predictably resulted in the differentiation of both stem cell populations. Umezawa teaches that, optimally, 3 μmol/L of 5-acacytidine is used to differentiate bone marrow stem cells, *see* "best mode" described in Example 1 of Umezawa. Alternatively, Rangappa teaches that no transformation of fat-derived stem cells occurs at this 5-acacytidine concentration, *see* page 778, left column and Table 2 of Rangappa. Accordingly, the optimal conditions for transformation of bone marrow stem cell differentiation are different from the optimal conditions for differentiation of fat-derived stem cells. Based upon the foregoing, an ordinary artisan could not have reasonably predicted that conditions could be optimized such that both stem cell populations could have differentiated into cardiomyoctyes under the same conditions, rendering the reason for combining the two stem cell populations invalid.

8. The teachings of Egger, Bonnet, Gilmore and Lee fail to remedy the deficiencies of Umezawa and Rangappa. These references are merely cited for describing the function of 5-azacytidine or to describe elements in the dependent claims.

9. Based upon the foregoing, I do not believe that the Examiner's rationale for combining the two stem cell populations is reasonable. An ordinary artisan could not have reasonably expected that bone marrow stem cells and fat-derived stem cells could have been cultured at the same time and under the same conditions to obtain a useful cardiomyoctye population. The different rates of differentiation and different optimal culturing requirements would not have allowed an ordinary artisan to reasonably expect that such a result could have been achieved.

STATEMENT UNDER 18 U.S.C. § 1001

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: Robert W Fabian Date: September 14, 2009